PATENTS • DESIGNS • COPYRIGHT • TRADE MARKS
The Patent Office

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed P. Mahoney

Dated 29 MAY 2001

THE PATENT OFFICE
18 AUG 1998
RECEIVED BY HAND

Pat Form 1/77

Patents Act 1977
(Rule 16)

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference

NCB/P21181GB

2. Patent application number
(The Patent Office will fill in this part)

9818023.5

3. Full name, address and postcode of the or of each patent applicant *(underline all surnames)*

QUEEN MARY & WESTFIELD COLLEGE

Mile End Road
London E1 4NS

Patents ADP number *(if you know it)* 05612072001.

If the applicant is a corporate body, give the country/state of its incorporation GB

4. Title of the invention

CANCER TREATMENT.

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

KILBURN & STRODE
20 RED LION STREET
LONDON
WC1R 4PJ

Patents ADP number *(if you know it)* 125001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application number	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

YES

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body. See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	:	0
Description	:	13
Claim(s)	:	1
Abstract	:	-
Drawing(s)	:	3 + 3

10. If you are also filing any of the following, state how many against each item.

Priority documents	:	-
Translations of priority documents	:	-
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	:	-
Request for preliminary examination and search *(Patents Form 9/77)*	:	-
Request for substantive examination *(Patents form 10/77)*	:	-
Any other documents *(please specify)*	:	-

11. I/We request the grant of a patent on the basis of this application.

Signature: Kilburn & Strode

Date: 18 August 1998

12. Name and daytime telephone number of person to contact in the United Kingdom

Nick C. Bassil
Tel: 0171-539 4200

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered `Yes' Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

f) For details of the fee and ways to pay please contact the Patent Office.

CANCER TREATMENT

The present invention relates to the use of angiotensin in a method for the treatment or prevention of cancer.

The renin-angiotensin system (RAS) is the name given to the system of substrates and enzymes that gives rise to the active circulating hormone, angiotensin II. Renin is a proteolytic enzyme secreted into the bloodstream by the juxtaglomerula cells of the kidney. It cleaves a substrate, angiotensinogen, which is a component of the α_2-globulin fraction of the plasma proteins to yield a decapeptide called angiotensin I. Two amino acids from the carboxyl terminus of this peptide are, in turn, cleaved by angiotensin converting enzyme (ACE) to produce the active octapeptide angiotensin II:

Asp-Arg-Val-Tyr-Ile-His-Pro-Phe

Other enzymes may act on angiotensin I or II to yield angiotensin III (des-Asp^1-angiotensin II) or angiotensin 1-7, but is generally thought that angiotensin II has the greatest biological significance (Vinson *et al Mol. Medicine Today* **1** 35-38 (1995)). Using *in situ* hybridisation methods, it has been shown that the prorenin gene is actively transcribed in fibroblasts surrounding the breast ducts in normal tissue. This arrangement becomes distorted in the cancerous breast, in which prorenin gene transcription becomes attenuated, and may cease altogether (Tahmasebi *et al Eur. J. Cancer* - in press (1998)).

Historically, angiotensin II has been recognised for its central role in mammalian electrolyte homeostasis and haemodynamics (Peach, M. T., *Physiol. Rev.* **57** 313-370 (1977)), particularly through the regulation of aldosterone secretion and cardiovascular function. At a pathological level, the RAS has a significant role in

hypertension: ACE antagonists are a valuable tool in the treatment of this disease (Ferrario, C. M., *J. Cardiovasc. Pharmacol.* **15** (Suppl. 3) S1-S5 (1990)). The genes encoding both ACE and angiotensin are considered to be candidates contributing to the pathogenesis of hypertension and cardiovascular disease (Jeunemaitre *et al Cell* **71** 169-180 (1992)).

Angiotensin exerts is biological effects via specific receptors of which there are two main subtypes classified as AT_1 and AT_2. Most of the known physiological functions of angiotensin II appear to be mediated via the AT_1 receptor, but the widespread incidence of the AT_2 receptor suggests that it has specific roles (Vinson *et al Mol. Medicine Today* **1** 35-38 (1995)). The AT_1 receptor is widely distributed in many tissue types and appears to be particularly abundant in epithelial tissue. The AT_1 receptor has also found to be present at a higher than normal density in breast cancer epithelial cells leading to the suggestion that AT_1 receptors may have a functional bearing on the development of breast cancer (Vinson *et al Mol. Medicine Today* **1** 35-38 (1995)), or that angiotensin may be involved in the development of cancer (Vinson *et al B. J. Cancer* **75** (9) 1279-1283 (1997)).

As a cause of mortality, cancer is second only to cardiovascular disease. The commonest sites of cancer in populations in Europe or North America are lung, skin, large bowel, prostate, stomach, rectum in men, and breast, large bowel, skin, lung and cervix in women. The overall mortality rates may, though, be different from the incidence rates. Cancer incidence also shows a variation geographically with certain countries or areas having rates of incidence for certain types of cancer. To date, many factors have been identified as being responsible for the development of cancer and these include: chemical carcinogens, irradiation (ionising radiation and UV radiation, including sunlight), viruses and genetic factors. Cancer cells that proliferate in the body but stay together form benign tumours; those that not only

proliferate but also shed cells, e.g. via the blood or lymphatic system (metastasis) to form colonies elsewhere form malignant tumours.

Metastasis is a remarkable process and one which is still poorly understood. The risk of metastases increases as tumours become larger. The cells must survive tissue invasion, circulation, passage across the capillary wall, and establishment in tissues. The process of tissue penetration appears to be by secretion of enzymes known as metalloproteinases (such as collagenase). The precise location of a metastasis is probably due in part to chance. However, clinical patterns of blood-borne metastasis have been observed. For example, gut cancers spread through the portal venous system to the liver; ovarian cancers seed into the peritoneal space; breast cancer has a tendency to spread to the bones of the axial skeleton; and sarcomas often spread into the lung (Souhami, R. L. and Moxham, J., *Textbook of Medicine*, Second edition, Churchill Livingstone, New York (1994)). A long term goal in the treatment of cancer is the prevention of the spread of the primary tumour by metastasis and the development of secondary tumours elsewhere in the body.

A key feature of metastasis is a disruption of the normal regulation of the integrin class of cell adhesion molecules. The integrins are members of a large family of cell adhesion molecules which include the cadherins, selectins and immunoglobulins. The integrins are receptors that normally modulate cell-matrix as well as cell-cell adhesion and play an important part in a diverse range of biological processes including organogenesis, growth and inflammation by influencing cell migration, anchorage and differentiation (Albelda, S. M. and Buck, C. A., *FASEB J.* **4** 2868-2880 (1990)). A disturbance in the normal control of integrin function predisposes to pathological conditions, including tumour invasion and metastasis (Hart, I. R. and Saini, A., *Lancet* **329** 1453-1461 (1992)). During tumour progression, cell adhesion activity is involved in altered (i) cell-cell and (ii) cell-substratum attachment, and (iii)

cell migration and invasion through basement membranes, thereby releasing tumour cells into the circulation or lymphatic system. These three processes are probably mediated by different receptors (Zhang *et al J. Cell Biol.* **122** 235-242 (1993)). Each process thus forms a different step of the metastatic cascade and a combination of all three is likely to be required for metastasis to occur. The various cell adhesion molecule families probably act in conjunction since current evidence cannot attribute this complicated process to a single sub-group.

Integrins are transmembrane receptors, each one being a glycoprotein heterodimer consisting of varying α- and β-subunits. Fourteen α- and eight β-subunits have been described and these associate to form 20 known integrins (Hynes, R. O. *Cell* **69** 11-25 (1992)). The integrins recognise a variety of important basement membrane and matrix proteins including laminin, collagen, fibronectin and vitronectin (Ruoslahti, E. and Pierschbacher, M. D., *Science* **238** 491-497 (1987); Yamada *et al Cancer Res.* **50** 4485-4496 (1990)).

In glandular epithelium, the principle integrins are members of the β_1, β_3, β_4 and β_5 subfamilies and selective loss of their expression in primary breast cancer cells has been described. In addition, a significant relationship has been shown between loss of specific integrin expression on primary breast cancer cells and the presence of axillary nodal metastasis. More importantly, using malignant epithelial cells taken directly from these patients, it has been discovered that both the specific integrin loss and lymph node invasion are related to reduced adhesive properties of those cells derived from patients with nodal metastasis.

It has now been surprisingly discovered that angiotensin induces integrin production in cancer cells in contrast to its previously supposed role and that as a result angiotensin can inhibit cancer cell invasiveness.

According to first aspect of the present invention there is provided a method of treatment or prevention of metastasis of cancer cells comprising the step of administering to a patient in need of treatment an effective amount of an angiotensin. This aspect of the invention also extends to the use of an angiotensin in the preparation of a medicament for the prevention or treatment of metastasis of cancer cells.

The present invention therefore offers a significant advance in the treatment of cancer which should permit the early and effective treatment of aggressive malignant tumours in preventing or inhibiting the spread from the primary tumour location. Angiotensin is a naturally occurring biologically active molecule which should be tolerated well by the body in contrast to existing chemotherapeutic agent or radiotherapy currently used to treat cancer.

In the present invention, the angiotensin molecule may be angiotensin II, although it is envisaged that alternative synthetic forms of the hormone could be made by substitution of one or more amino acids in the molecule. The invention therefore extends to the use of a molecule having angiotensin activity. The skilled person is aware that various amino acids have similar properties. One or more such amino acids of a substance can often be substituted by one or more other such amino acids without eliminating a desired activity of that substance. Thus the amino acids glycine, alanine, valine, leucine and isoleucine can often be substituted for one another (amino acids having aliphatic side chains). Of these possible substitutions it is preferred that glycine and alanine are used to substitute for one another (since they have relatively short side chains) and that valine, leucine and isoleucine are used to substitute for one another (since they have larger aliphatic side chains which are hydrophobic). Other amino acids which can often be substituted for one another include: phenylalanine, tyrosine

and tryptophan (amino acids having aromatic side chains); lysine, arginine and histidine (amino acids having basic side chains); aspartate and glutamate (amino acids having acidic side chains); asparagine and glutamine (amino acids having amide side chains); and cysteine and methionine (amino acids having sulphur containing side chains). Substitutions of this nature are often referred to as "conservative" or "semi-conservative" amino acid substitutions.

Amino acid deletions or insertions may also be made relative to the amino acid sequence of angiotensin. Thus, for example, amino acids which do not have a substantial effect on the activity of angiotensin, or at least which do not eliminate such activity, may be deleted. Amino acid insertions relative to the sequence of angiotensin can also be made . This may be done to alter the properties of a substance of the present invention (e.g. to assist in identification, purification or expression, where the protein is obtained from a recombinant source, including a fusion protein. Such amino acid changes relative to the sequence of angiotensin from a recombinant source can be made using any suitable technique e.g. by using site-directed mutagenesis. The angiotensin molecule may, of course, be prepared by standard chemical synthetic techniques, e.g. solid phase peptide synthesis, or by available biochemical techniques, e.g. enzymatic treatment of angiotensinogen with renin.

It should be appreciated that amino acid substitutions or insertions within the scope of the present invention can be made using naturally occurring or non-naturally occurring amino acids. Whether or not natural or synthetic amino acids are used, it is preferred that only L-amino acids are present.

Whatever amino acid changes are made (whether by means of substitution, insertion or deletion), preferred polypeptides of the present invention have at least 50% sequence identity with a polypeptide as defined in a) above more preferably the degree of

sequence identity is at least 75%. Sequence identities of at least 90% or at least 95% are most preferred.

The degree of amino acid sequence identity can be calculated using a program such as "bestfit" (Smith and Waterman, Advances in Applied Mathematics, 482-489 (1981)) to find the best segment of similarity between any two sequences. The alignment is based on maximising the score achieved using a matrix of amino acid similarities, such as that described by Schwarz and Dayhof (1979) Atlas of Protein Sequence and Structure, Dayhof, M.O., Ed pp 353-358. Where high degrees of sequence identity are present there will be relatively few differences in amino acid sequence.

Metastasis of cancer cells is the process by which cancer cells from a malignant primary tumour invade the surrounding tissue and spread out into the body to seed secondary tumours. Secondary tumours are also capable of undergoing metastasis to spread further. Metastasis can also be characterised as the invasiveness potential of a cancer tumour. A method or use in accordance with this aspect of the invention can therefore be used to reduce and/or inhibit the invasiveness potential of a cancer cell.

The present invention will be generally applicable to all forms of cancer, but it is to breast cancer that the invention should find particular utility. Other cancers which may be treated include, but are not limited to, skin cancer (melanoma), large bowel cancer, prostate cancer, lung cancer, bone cancer, or cancer of the cervix, stomach, or rectum.

A medicament comprising an angiotensin may be prepared by standard pharmaceutical techniques known in the art depending upon the mode of administration and the particular disease to be treated. The medicament will usually

be supplied as part of a sterile, pharmaceutical composition which will normally include a pharmaceutically acceptable carrier. This pharmaceutical composition may be in any suitable form, (depending upon the desired method of administering it to a patient). It may be provided in unit dosage form, will generally be provided in a sealed container and may be provided as part of a kit. Such a kit would normally (although not necessarily) include instructions for use. It may include a plurality of said unit dosage forms.

The pharmaceutical composition may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such compositions may be prepared by any method known in the art of pharmacy, for example by admixing the active ingredient with the carrier(s) or excipient(s) under sterile conditions.

Pharmaceutical compositions adapted for oral administration may be presented as discrete units such as capsules or tablets; as powders or granules; as solutions, syrups or suspensions (in aqueous or non-aqueous liquids; or as edible foams or whips; or as emulsions). Suitable excipients for tablets or hard gelatine capsules include lactose, maize starch or derivatives thereof, stearic acid or salts thereof. Suitable excipients for use with soft gelatine capsules include for example vegetable oils, waxes, fats, semi-solid, or liquid polyols etc. For the preparation of solutions and syrups, excipients which may be used include for example water, polyols and sugars. For the preparation of suspensions oils (e.g. vegetable oils) may be used to provide oil-in-water or water in oil suspensions. In certain situations, delayed release preparations may be advantageous and compositions which can deliver an angiotensin in a delayed or controlled release manner may also be prepared. Prolonged gastric residence brings

with it the problem of degradation by the enzymes present in the stomach and so enteric-coated capsules may also be prepared by standard techniques in the art where the angiotensin is for release lower down in the gastro-intestinal tract.

Pharmaceutical compositions adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in *Pharmaceutical Research*, **3(6)**:318 (1986).

Pharmaceutical compositions adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils. For infections of the eye or other external tissues, for example mouth and skin, the compositions are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base. Pharmaceutical compositions adapted for topical administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent. Pharmaceutical compositions adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical compositions adapted for rectal administration may be presented as suppositories or enemas.

Pharmaceutical compositions adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid

inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable compositions wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical compositions adapted for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulizers or insufflators.

Pharmaceutical compositions adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical compositions adapted for parenteral administration include aqueous and non-aqueous sterile injection solution which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation substantially isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Excipients which may be used for injectable solutions include water, alcohols, polyols, glycerine and vegetable oils, for example. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carried, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

The pharmaceutical compositions may contain preserving agents, solubilising agents, stabilising agents, wetting agents, emulsifiers, sweeteners, colourants, odourants, salts (substances of the present invention may themselves be provided in the form of a pharmaceutically acceptable salt), buffers, coating agents or antioxidants. They may

also contain therapeutically active agents in addition to the substance of the present invention.

Dosages of the substance of the present invention can vary between wide limits, depending upon the disease or disorder to be treated, the age and condition of the individual to be treated, etc. and a physician will ultimately determine appropriate dosages to be used.

Without wishing to be bound by theory, it is believed that the angiotensin molecule is promoting cell adhesion by inducing the expression of integrin production in cancer cells. An increase in cell adhesion being mediated by integrin molecules thus leading to a reduced chance for metastasis of cancer cells from a tumour.

According to a second aspect of the present invention there is provided a method of inducing expression of β_1 integrin molecules in cancer cells comprising the step of administering to a patient an effective amount of an angiotensin. This aspect of the invention also extends to the use of an angiotensin in the preparation of a medicament for the induction of expression of β_1 integrin molecules in cancer cells.

As described above, the integrin molecules form part of a larger superfamily of related cell adhesion molecules. The β_1 integrin subunit is found in combination with various α-subunits as follows: $\beta_1\alpha_1$ (ligands include collage type-I, -IV, -VI, laminin P1 and E1); $\beta_1\alpha_2$ (ligands include collagen type-I, -IV, laminin, fibronectin); $\beta_1\alpha_3$ (ligands include fibronectin, collagen type-I, laminin (E3), epiligrin; $\beta_1\alpha_4$ (ligands include fibronectin, VCAM-1); $\beta_1\alpha_5$ (ligands include fibronectin); $\beta_1\alpha_6$ (ligands include laminin (E8)); $\beta_1\alpha_7$ (ligands include laminin (E8)); and $\beta_1\alpha_8$ (ligands include fibronectin).

A method or use in accordance with this aspect of the present invention has the advantage of promoting the expression of integrin molecules on cancer cells which can reduce or inhibit the invasiveness potential of the cancer cells. In other words, the promotion of expression of integrin expression can prevent or treat metastasis of cancer cells.

Preferred features for the second and subsequent aspects of the invention are as for the first aspect *mutatis mutandis*.

The present invention will now be described with reference to the following examples and drawings which are present for the purposes of illustration and are not to be construed as being limiting on the invention. In the examples reference is made to a number of drawings, in which:

FIGURE 1 shows images of MCF-7 cancer cell line preparations having undergone immunocytochemistry for the β_1 integrin subtype (x40 magnification).

FIGURE 2 shows a digitised image of a gel autoradiograph demonstrating relative increase in density of angiotensin II (A II) pre-treated protein band compared to control under non-reducing conditions.

FIGURE 3 shows a graph of the effect of angiotensin II on breast cancer cell invasion in which inhibition of IGF-I stimulated invasion after pre-treatment with angiotensin II (A II) is compared to a control without A II treatment.

Example 1: Immunocytochemical study of effect of Angiotensin II on β_1 integrin expression in MCF-7 cancer cell line

The effect of Angiotensin II on β_1 integrin expression in MCF-7 subtype cancer cell line was studied using immunocytochemistry and the results are shown in Figure 1. The evident increase in staining of cells treated with angiotensin II (A II) at 10^{-5}M demonstrates the increase expression of β_1 integrin protein.

Example 2: Labelling of β_1 integrin protein with I^{125}

Cell surface proteins were labelled with I^{125} to study expression of the β_1 integrin subtype. After labelling, the β_1 integrin was immunoprecipitated with an anti-β_1 integrin antibody. Figure 2 shows the result of an autoradiograph demonstrating the increased expression of β_1 integrin after treatment with angiotensin II (A II) compared to a control sample.

Example 3: Effect of Angiotensin II on breast cell cancer invasion

The effect of angiotensin II (A II) in inhibiting growth factor-induced stimulated cancer cell invasiveness was studied as a model system and the results are shown in Figure 3. The study was carried out using an invasion chamber in which two compartments are separated by a perforated membrane coated in matrix protein. A chemoattractant, IGF-I, was added to the medium on one side of the chamber, and the breast cancer cells to the other. Invasiveness was measured by counting the cells that migrated from one chamber to the other. Treating the cells with angiotensin II (A II) prior to the invasion assay led to a tenfold reduction in mean invasion from 1.58% to 0.15% ($p = 0.0011$). The invasiveness potential of the cancer cells was therefore markedly inhibited by angiotensin II.

CLAIMS

1. A method of treatment or prevention of metastasis of cancer cells comprising the step of administering to a patient in need of treatment an effective amount of an angiotensin.

2. A method as claimed in claim 1, in which the cancer cell is derived from breast, skin, large bowel, prostate, lung, bone, cervix, stomach, or rectum.

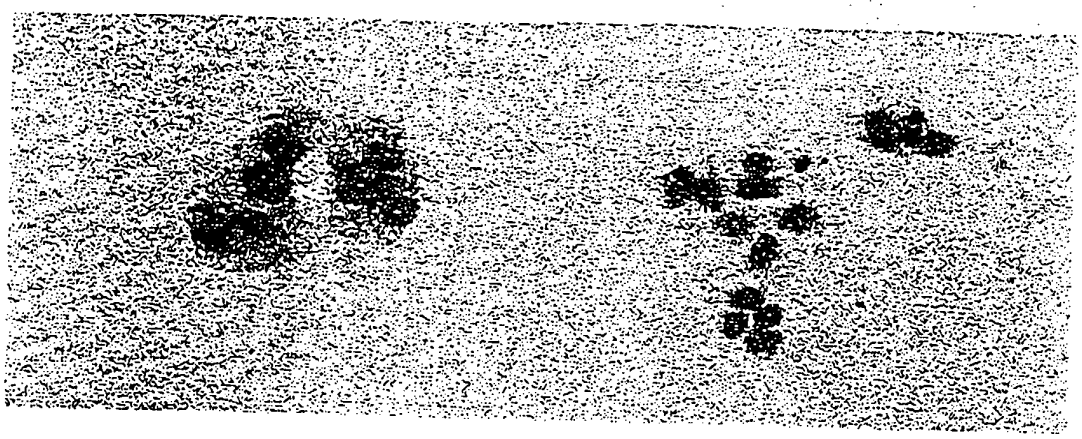
3. A method as claimed in claim 1 or claim 2, in which the angiotensin is angiotensin II.

4. The use of an angiotensin in the preparation of a medicament for the prevention or treatment of metastasis of cancer cells.

5. A use as claimed in claim 4, in which the medicament is for oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) administration.

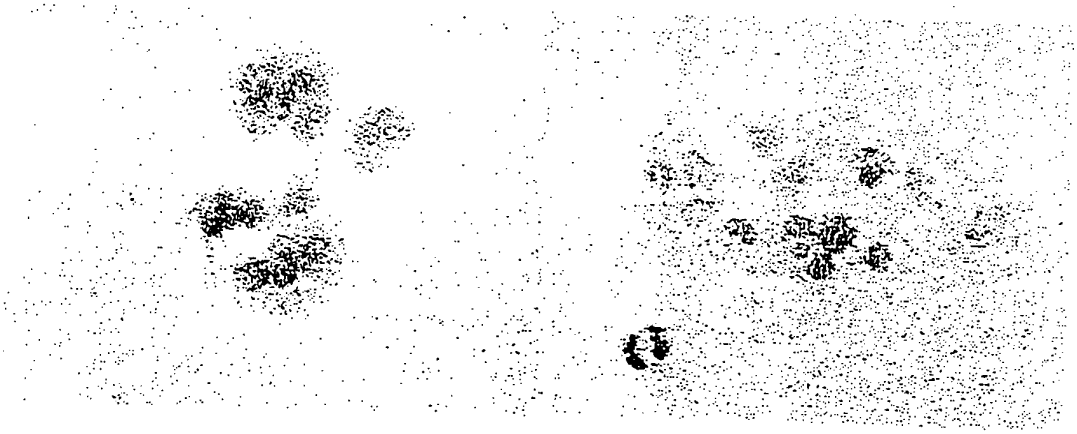
6. A method of inducing expression of β_1 integrin molecules in cancer cells comprising the step of administering to a patient an effective amount of an angiotensin.

7. The use of an angiotensin in the preparation of a medicament for the induction of expression of β_1 integrin molecules in cancer cells.



A II-pretreated; anti-β1 +ve

A II-pretreated; anti-β1 -ve



A II untreated; anti-β1 +ve

A II untreated; anti-β1 -ve

FIGURE 1

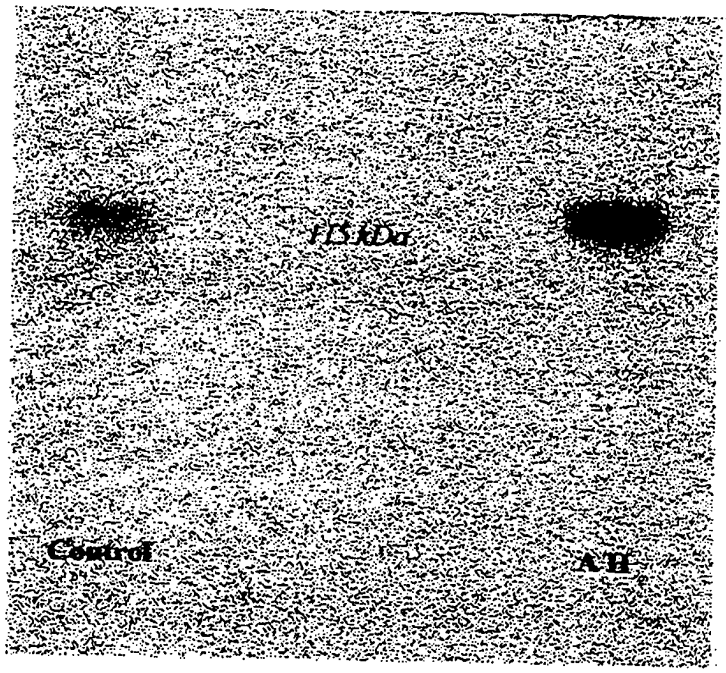


FIGURE 2

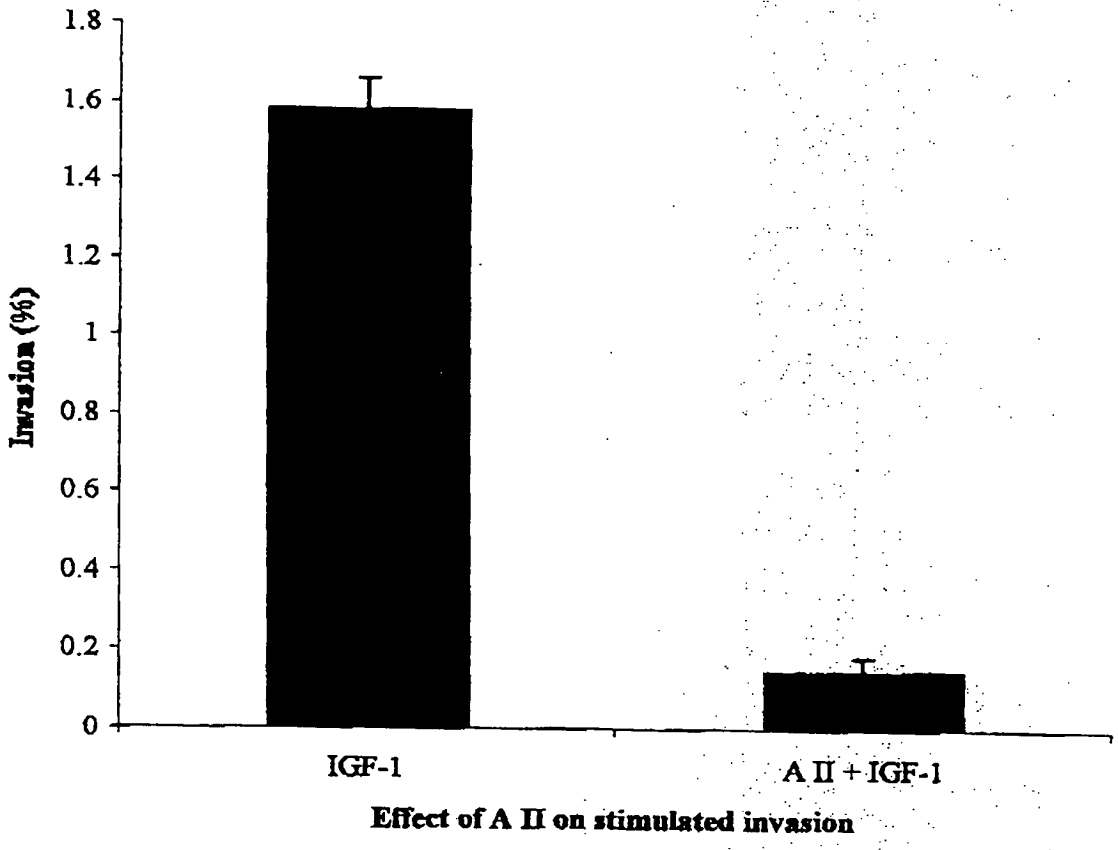

1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Invasion (%)
IGF-1
A II + IGF-1
Effect of A II on stimulated invasion

FIGURE 3